REMARKS

Claims 1, 3, 4, 6-12, 14-18, 20, 22, 36-38, and 40-47 are pending. Claims 2, 5, 13, 19, 21, 25-35, and 39 are cancelled. Claims 10-12, 22, and 47 are withdrawn.

Applicants thank the Examiner for the courtesy extended during the interview on July 22, 2008. Applicants appreciate the Examiner's acknowledgment that the proposed amendment to claim 1 would be entered after final to place the claims in better condition for appeal. This amendment reduces the scope of generic claim 1 from all lysosomal storage disorders to a group consisting of Fabry disease, Niemann-Pick disease, Pompe disease, and Gaucher disease and makes clear that the lysosomal hydrolase administered to the subject corresponds to the lysosomal hydrolase that is deficient in the subject. Support for this amendment can be found throughout the specification as filed. This amendment should not be construed as acquiescence to the rejection. Applicants fully intend to pursue the broader subject matter in a continuation application.

The amendment to claim 1 does not violate Applicants' election of claims 1-9, 13-18, and 20-21, drawn to a method of treating a subject having a lysosomal storage disorder, *such as* Fabry disease, comprising administering a gene therapy vector and an exogenously produced natural or recombinant lysosomal hydrolase, such as alpha-galactosidase. In the restriction requirement issued April 10, 2006, the Examiner indicated that claims 1, 2, 3, 4, 5, 6, 7-9, 10-12, 13-18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29-32, 33, and 34 were all linking claims that linked the various inventions and that the restriction requirement *was subject to non-allowance of the linking claims.* April 10, 2006, Restriction Requirement at 5. Because claim 1 has always been a linking claim

between claim group I (gene therapy + enzyme replacement therapy for Fabry) and group IV (gene therapy + enzyme replacement therapy for Pompe), and because claims to methods of treating Niemann-Pick disease (claims 42-44) and Gaucher disease (claims 45-46) have already been considered by the Examiner (Office Action at 1, 2, and 3), the amendment to claim 1 does not change the linking nature of this claim. Accordingly, the amendment should be entered.

Claims 8 and 38 are amended to correct a minor typographical error in the spelling of the replacement enzyme substrate. Withdrawn claim 22 is amended to make it consistent with claim 1.

None of the amendments to the claims raises the issue of new matter. Nor do the amendments present new issues requiring further consideration or search. Applicants submit that the amendments place the application in condition for allowance or in better form for appeal.

The Examiner indicated that he was unable to locate evidence of FDA approval of various replacement enzymes. Office Action at 7. Although most of these approvals are evidenced in the references of record, Applicants have provided with this response copies of the proscribing information for Cerezyme®, Myozyme®, Aldurazyme®, Elaprase® and Naglazyme™.

Rejection under 35 U.S.C. § 112, First Paragraph

In the Office Action of February 12, 2008, the Examiner rejects claims 1, 3, 4, 6-9, 14-18, 20, 36-38, and 40-46 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

The standard for establishing enablement is whether or not the specification teaches a person skilled in the art how to practice the invention without undue experimentation. See, e.g., *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). An invention is not invalid for lack of enablement even if some experimentation is required to practice the invention, particularly if the experimentation would be routine to persons skilled in the art. See, e.g., *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558 at 1564 (Fed. Cir. 1996). To determine whether or not the amount of experimentation is undue, eight factors may be considered, including:

(1) the quantity of experimentation necessary;

(2) the amount of direction or guidance presented;

(3) the presence or absence of working examples;

(4) the nature of the invention;

(5) the state of the prior art;

(6) the relative skill of those in the art;

(7) the predictability or unpredictability of the art; and

(8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). Not all of these factors need be present. What is relevant depends on the facts. *See, e.g., Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The Claimed Invention

The standard treatment for many lysosomal storage disorders (LSDs), when a source of the deficient enzyme is available, is enzyme replacement therapy (ERT). Specification at paragraph [013]. Several lysosomal hydrolases are commercially

available for the treatment of lysosomal storage disorders, such as, e.g. glucocerebrosidase (Cerezyme®) for the treatment of Gaucher's disease, α-galactosidase (Fabrazyme®) for the treatment of Fabry disease, α-L-iduronidase (Aldurazyme®) for the treatment of MPS I (Hurler disease), iduronate sulfatase (Elaprase®) for the treatment of MPS II (Hunter disease), arylsulfatase B (Naglazyme™) for the treatment of MPS VI (Maroteaux-Lamy disease), and α-glucosidase (Myozyme®) for the treatment of Pompe disease. Clinical trials are currently underway with the replacement enzyme sphingomyelinase for the treatment of Niemann-Pick B disease.

Unfortunately, enzyme replacement therapy can sometimes lead to an immune reaction to the replacement enzyme, making therapy less effective and/or requiring larger amounts of enzyme to achieve the necessary treatment goal. Specification at paragraph [018]. See also, *Wraith 2006* (previously submitted) at 446. In some cases, this means that manufacturers of replacement enzymes have difficulty meeting the clinical demand for the replacement enzymes.

Applicants' invention provides a means of alleviating this problem. Applicants have discovered that by first administering to a patient suffering from a lysosomal storage disorder the missing or defective lysosomal hydrolase via gene therapy, the patient develops an immune tolerance to the enzyme, without the need to suppress the immune system. Then, when traditional enzyme replacement therapy is administered, the patient will have a reduced immune reaction to the replacement enzyme. Specification at Examples 8 and 9. This allows the replacement enzyme to work better and consequently to be administered in lower doses. Specification at paragraphs

[0182] and [0183]. The claimed invention has also been shown to improve current treatment of lysosomal storage diseases by augmentation of ERT with prior administration of lysosomal hydrolase via gene therapy. Specification at Example 10.

Thus, the claims are directed to methods of treating a subject diagnosed with a lysosomal storage disorder selected from Fabry disease, Pompe disease, Gaucher disease and Niemann-Pick disease, comprising first administering an adeno-associated virus (AAV) gene therapy vector encoding the deficient lysosomal hydrolase under the control of a liver specific regulatory element, and then administering an exogenously produced natural or recombinant form of that lysosomal hydrolase, such that the lysosomal storage disorder is treated. Applicants have provided evidence of *in vivo* efficacy of the claimed method for each of the recited lysosomal storage disorders. Applicants submit that the standard for enablement, as applied to the claimed invention, has been met by the specification and subsequent demonstration of efficacy.[1]

Scope of the Claims

The Examiner contends that "[t]he claims read on using polynucleotides encoding various lysosomal hydrolases to treat various lysosomal storage diseases," and that "this includes treating a lysosomal storage disease with a *non-corresponding* lysosomal hydrolase." Office Action at 4 (emphasis added). The Examiner states that "[t]he specification fails to provide adequate guidance and evidence for how to treat

[1] Applicants emphasize that the amendment and arguments made in this response are not to be construed as an admission that the specification is not enabling for treatment of the broader genus of lysosomal storage disorders. The four representative examples of successful application of the claimed methods of treatment provided by Applicants should be more than sufficient to enable the generic invention. Applicants have limited the claims to treatment of those four exemplified diseases only to facilitate allowance of the claims or to narrow the issues on appeal.

different lysosomal storage disease with a non-corresponding lysosomal hydrolase and how to treat lysosomal storage disease with an unknown cause." *Id.* Applicants traverse.

The Examiner has not considered enablement from the point of view of the person of skill in the art. Claims are to be objectively construed in view of the knowledge of persons skilled in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313, (Fed. Cir. 2005) ("Patents are addressed to and intended to be read by others of skill in the pertinent art"); M.P.E.P. 2164.08(b). Persons skilled in the art, i.e., those having experience in the art of treating and/or investigating lysosomal storage disorders and knowledge of the underlying mechanisms of pathogenesis for these diseases, would readily appreciate which lysosomal hydrolase deficiency is associated with a specific lysosomal storage disorder. Accordingly one of skill in the art would know that administration of the deficient lysosomal hydrolase is the best choice to treat the specific lysosomal storage disorder in the claimed invention. Any assertion to the contrary is simply unsupportable.

One of skill in the art, reading Applicants' claims, would not attempt to treat a lysosomal storage disorder without knowing what lysosomal hydrolase deficiency or what malfunction is responsible for the disease. Nor would one of skill in the art, knowing that α-galactosidase is the enzyme that is missing or defective in patients with Fabry disease, attempt to treat Fabry disease with glucocerebrosidase, the lysosomal hydrolase that is deficient in patients with Gaucher's disease. Not only does the skilled artisan know which lysosomal hydrolase should be used to treat a specified deficiency, the specification provides this information as well. For example, paragraph [003] of the

specification teaches that each of the over thirty known lysosomal storage disorders is characterized by a compromised lysosomal hydrolase. Table 1 (paragraph [086]) and paragraphs [004] to [012] list various lysosomal storage diseases and the enzyme deficiency associated with each.

The law does not require claims to eliminate non-working embodiments particularly where, as here, one of skill in the art would readily appreciate that such embodiments (i.e., treatment of an LSD with a non-corresponding enzyme) are not likely to work. *Atlas Powder Co v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984). To fully comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, the specification need only be enabling *to one of ordinary skill in the art*. With Applicants' specification in hand, it is well within the skill of a person in the art to select an appropriate lysosomal hydrolase to treat a particular lysosomal storage disorder. Thus, the specification meets the requirements of 35 U.S.C. § 112, first paragraph.

Moreover, claim 1, by its own terms, does not encompass non-working embodiments. The claim requires that *the lysosomal storage disease is treated*. Thus, any treatment method encompassed by claim 1 must actually *treat* the lysosomal storage disease in question. Fabry disease will not be treated by administration of glucocerebrosidase. Nor would other lysosomal storage disorders be treated with a non-corresponding lysosomal hydrolase. Thus, contrary to the Examiner's contention, claim 1 *does not* encompass treatment of *any* lysosomal storage disorder with *any* lysosomal hydrolase, including a non-corresponding lysosomal hydrolase; it

encompases treatment of a lysosomal storage disorder with a lysosomal hydrolase that is *effective to treat* that storage disease.

However, *without acquiescing* to the Examiner's argument, and merely to facilitate allowance of the claims, Applicants have amended claim 1 to make it clear that the claimed methods of treatment involve administration of the lysosomal hydrolase that deficient in the subject being treated. Applicants also note that the Examiner's assertion that the claims read on using polynucleotides encoding various lysosomal hydrolases, including non-corresponding lysosomal hydrolases, to treat various lysosomal storage diseases, does not apply to claim 20, and dependent claims 36-38, 40 and claim 44. These claims are directed to methods of treating a specific lysosomal storage disease (Fabry disease) by administering a gene therapy vector encoding the specific lysosomal hydrolase (α-galactosidase A) that is deficient in subjects suffering from that specific disease.

Accordingly, Applicants request that the Examiner withdraw this basis for rejection of the claims.

State of the Art

A. Treatment of Lysosomal Storage Disorders

1) "Treatment" Does Not Require Total Elimination of Disease

The Examiner states that the claims are not enabled because "the multisystemic nature of lysosomal storage disorders and the possibility of 'sanctuaries' . . . raises the prospect that only *partial responses* may occur, despite prolonged treatment." Office Action at 5 (emphasis added). The Examiner contends that although reduction of accumulated metabolites in lysosomal storage disorders may be a good beginning to

treat lysosomal storage disorders, this does not mean that the diverse pathological symptoms of various lysosomal storage disorders would be ameliorated. Office Action at 9. Further, the Examiner alleges that the fact that "'treatment of non-CNS aspects of a LSD may be helpful to patients exhibiting neurological symptoms' does not mean that the claimed invention is enabled." Office Action at 11. Applicants respectfully traverse.

Applicants note that each of the lysosomal storage disorders recited in claim 1 corresponds to a lysosomal hydrolase that has been demonstrated to be effective to treat its corresponding lysosomal storage disorder when administered to a patient or an art-recognized animal model. As discussed above, the FDA has approved numerous lysosomal hydrolases for enzyme replacement therapy in patients with corresponding lysosomal storage disorders, including glucocerebrosidase (Cerezyme®) for the treatment of Gaucher's disease, α-galactosidase (Fabrazyme®) for the treatment of Fabry disease, α-L-iduronidase (Aldurazyme®) for the treatment of MPS I (Hurler disease), iduronate sulfatase (Eleprase®) for the treatment of MPS II (Hunter disease), arylsulfatase B (Naglazyme™) for the treatment of MPS VI (Maroteaux-Lamy disease), and α-glucosidase (Myozyme®) for the treatment of Pompe disease. These replacement enzymes are currently being used to treat thousands of LSD patients. In addition, clinical trials are currently underway with the replacement enzyme sphingomyelinase for the treatment of Niemann-Pick B disease.[2]

[2] The Examiner contends that availability of an FDA approved treatment of a lysosomal storage disorder does not mean that the lysosomal storage disorder can be treated. Office Action at 7. Not only is this contention clearly at odds with the laws governing the FDA and its mandate, i.e., to ensure that drugs are safe and effective for their intended use (http://www.fda.gov/cder/regulatory/applications/laws.htm), it is simply wrong. Moreover, it is overwhelmingly contradicted by the evidence of record.

Applicants further note that the specification at paragraph [0186] defines the terms "treat," "treatment," and "treating" as meaning any of the following:

- reduction in severity of a disease or condition;
- reduction in the duration of a disease course;
- amelioration of one or more symptoms associated with a disease or condition;
- provision of beneficial effects to a subject with a disease or condition, without necessarily curing the disease or condition; or
- prophylaxis of one or more symptoms associated with a disease or condition.

Consequently, the claimed methods of treating a lysosomal storage disorder *do not* require that all of the "diverse pathological symptoms of various lysosomal storage disorders [be] ameliorated" as the Examiner contends. A patient suffering from one of the lysosomal storage disorders recited in claim 1 may be "treated" by the claimed methods if, e.g., he/she experiences some benefit from the treatment.

Those of skill in the art fully appreciate that for patients who suffer from a progressively debilitating lysosomal storage disorder, even partial treatment of symptoms can be beneficial to stabilize the condition, prevent further deterioration, and/or improve quality of life. For patients who have an LSD at birth, early treatment may prolong life and/or reduce the amount or severity of long-term developmental damage. For example, *Wraith 2006* at page 444 states that in his experience, "patients suffering from a progressive LSD would be happy if the treatment made the underlying condition stable and prevented further deterioration."

The Examiner contends that "'[i]mproved quality of life' does not mean that the LSD is treated and that pathological symptoms are ameliorated." Office Action at 11.

Applicants submit that those suffering from a lysosomal storage disorder or watching a friend or family member suffering, would disagree completely -- as would the medical community. Moreover, "improved quality of life" falls squarely within Applicants' definition of "treating" an LSD. Specification at paragraph [0186]. It is a well established principle of patent law that an Applicant is his own lexicographer. M.P.E.P. 2111.01 and 2173.05(a). The Examiner cannot impose his own definition for a term that is clearly defined in the specification *and* accepted by those of skill in the art.

Finally, the M.P.E.P. specifically teaches that "it is improper for Office personnel to request evidence . . . regarding the *degree* of effectiveness." M.P.E.P. 2107.03 (emphasis in original). "Office personnel should not . . . require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a . . . fully effective drug for humans." M.P.E.P. 2107.01. Indeed, "[a]n assertion that the claimed invention is useful in treating a symptom of an incurable disease may be considered credible . . . on the basis of a fairly modest amount of evidence or support." *Id.* In addition, Applicants note that considerations such as full safety and effectiveness are made by the FDA for approving therapeutics in clinical trials, and these considerations are different from those made by the PTO in determining whether a claim is enabled. *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

2) Despite Clinical Heterogeneity, LSDs Have a Common Underlying Mechanism

The Examiner contends that in view of the diversity of lysosomal storage disorders, the heterogeneity of clinical expression within lysosomal storage disorders, the limited number of enzyme replacement therapies available, and the difficulty of treating lysosomal storage disorders involving the central nervous system, a person of

skill in the art would not know how to treat lysosomal storage disorders. Office Action at 5. Applicants traverse.

Although lysosomal storage disorders may be "diverse," they share an underlying mechanistic similarity, i.e., the complete or partial lack of enzymatic activity of a particular lysosomal hydrolase. Lysosomal storage disorders are "a family . . . that result from different defects in lysosomal function." *Fauci* (previously submitted) at page 2169. Indeed, "[t]he clinical features of the lysosomal storage diseases can be *predicted* by knowing the normal site of degradation of the deficient enzyme's substrate and are dependent on the rate and magnitude of accumulation of undegraded material." *Id.* at page 2169 (emphasis added).

Applicants do not dispute that clinical heterogeneity is frequently observed. However, Applicants submit that it is well known to the skilled artisan that the heterogeneity of the clinical pathology of lysosomal storage disorders is largely due to varying amounts of build-up of substrate for the deficient lysosomal hydrolase, and it is the substrate build-up that can produce varying physiological effects throughout the body. Tissues that are most affected are those that contain the most accumulated substrate. *Salvetti* (previously submitted) at page 107. Genetic variations play a role in heterogeneity of lysosomal storage disorders. "In some cases, different mutations in the lysosomal structural genes account for the observed heterogeneity. For example, one mutation . . . may cause total loss of the enzyme activity, whereas another mutation . . . may result in only partial impairment of enzyme activity and a less severe clinical course." *Id.* at page 2169-70. In other cases, "[h]eterogeneity . . . is increased by the

fact that patients with autosomal recessive traits are frequently compound heterozygotes and inherit two different mutant alleles . . . ." *Id.* at page 2170.

Nevertheless, such heterogeneous clinical manifestations do *not* render treatment impossible or even uncertain. Generally, heterogeneous clinical manifestations do not necessitate heterogeneous treatments, although it may affect the frequency and/or course of treatment. Nor does the fact that heterogeneity exists suggest that Applicants' claims are not enabled. Rather, the skilled artisan would readily expect upon reading Applicants' specification that most, if not all, lysosomal storage disorders can be treated by supplying the missing or deficient enzymatic activity with an appropriate lysosomal hydrolase administered initially by gene therapy and then ERT. In fact, the efficacy of enzyme supplementation in treating lysosomal storage disorders, despite these heterogeneities, is evidenced, *inter alia*, by the FDA-approved ERTs listed above. Equally clear, from the approval of Cerezyme by the European equivalent of the FDA for type 3 (chronic neuropathic) Gaucher disease (http://www.emea.europa.eu/humandocs/PDFs/EPAR/Cerezyme/070697en1.pdf)(copy enclosed) , even lysosomal storage disorders that contain a central nervous system component are considered "treatable" with enzyme replacement therapy. Accordingly, Applicants submit that despite pathological heterogeneity and difficulties associated with treating CNS disorders, practice of the claimed treatment of a lysosomal storage disorder, and particularly the specific lysosomal storage disorders recited in claim 1, would not require undue experimentation.

3) LSD Metabolites Measure Treatment Progress

The Examiner contends that the reduction of accumulated metabolites in the organs of subjects with a lysosomal storage disorder does not indicate that pathological symptoms of various lysosomal storage disorders would be ameliorated or that the disease has been treated. Specifically, the Examiner argues that "GL-3 accumulation is only a metabolite accumulation due to the lack of alpha-Gal but not the pathological symptoms of the Fabry disease" and that "[t]here is no correlation between reduction of GL-3 level in the organs and treatment of Fabry disease", or between reduction of GL-1 and treatment of Gaucher disease. Office Action at 6-7. The Examiner is simply wrong.

Clinical pathology of lysosomal storage disorders is caused by build-up of the substrate for the deficient lysosomal hydrolase. Tissues that are most affected are those that contain the most accumulated substrate. *Salvetti* at page 107. It is well known to persons skilled in the art that the build-up of lysosomal metabolites is responsible for the damage to cells and results in the pathology of the lysosomal storage disorder. *See, e.g. Salvetti* at page 106 ("A deficiency in one of these [lysosomal hydrolase] digestion processes results in accumulation of the undegraded substrate within the lysosomes, which increase in number and size and can *severely impair* the physiology of the cell.") (emphasis added). See also specification at paragraph [005] ("Fabry disease is an X-linked recessive LSD characterized by a deficiency of α-galactosidase A . . . which leads to vascular and other disease manifestations *via accumulation* of glycosphingolipids . . . *such as GL-3*) (emphasis added). The specification also teaches that "accumulation of GL-3" is a measure of "disease progression" at paragraph [0104]. This is also the principle behind "substrate deprivation" therapy, which is discussed in the specification at paragraphs [021] to

[023]. In particular, paragraph [021] teaches that substrate deprivation therapy has been tested in humans with Gaucher disease, *resulting in an amelioration of symptoms.*

Additional evidence of the Examiner's misunderstanding is found in *Wraith 2006* (the first goal of an LSD treatment should be to reduce "the level of storage [metabolite] within the cells or organs of the individual," and "as a consequence . . . the natural history of the disease should be favorably altered"). See also, the Prescribing Information for Fabrazyme® (previously submitted), an FDA-approved lysosomal hydrolase for enzyme replacement therapy of Fabry Disease. The Prescribing Information characterizes reduction of "GL-3 inclusions" as the "*primary efficacy endpoint*" in clinical trials (emphasis added). Accordingly, with the specification in hand, one of skill in the art or one having even a rudimentary understanding of lysosomal storage diseases, would recognize the correlation of the accumulated metabolite and treatment of the corresponding lysosomal storage disorder and would expect that reduction of substrate build-up would indeed ameliorate lysosomal storage disorder symptoms.

4) Animal Models for LSDs Are Available

The Examiner also contends that there is a lack of suitable animal models for human lysosomal storage disorders to evaluate intravenous infusion of lysosomal enzymes (Office Action at 5). In doing so, the Examiner ignores evidence previously provided by Applicants that clearly refutes this contention. *See, e.g., Kikuchi* 1998 (ERT in quail model of Pompe disease); *Scaravilli and Suzuki* 1983 (ERT in murine model of Krabbe disease); *Kakkis* 1996 (ERT in canine model of MPS I); *Bielicki* 1999 (ERT in feline model of MPS VI); *Byers* 1997 (ERT in feline model of MPS VI); *Vogler* 1999 (ERT

in murine model of MPS VII); and *O'Connor* 1998 (ERT in murine model of MPS VII) (all previously submitted). *See also* specification at [018]-[020] and *Wraith 2006* (previously cited by the Examiner to support the *lack* of animal models)[3] at page 443, first column ("the identification and availability of animal models. . allowed for the first time new therapies [for LSDs] to be studied carefully in a preclinical setting"). Accordingly, Applicants submit that the Examiner's arguments regarding lack of animal models is clearly contradicted by the evidence of record.

B. Gene Therapy

At page 4, lines 11 to 16 of the Office Action, the Examiner contends that the claims read on *in vivo* gene therapy and that gene therapy was unpredictable at the time of the invention. Applicants disagree with Examiner's conclusion regarding gene therapy as it applies to the claimed invention.

Applicants' claims are not directed to gene therapy *per se*. Nor are the claims directed to treatment of lysosomal storage disorders using gene therapy alone. Rather, Applicants' invention is directed to a *combination therapy* (gene therapy + enzyme replacement therapy) that "*overcome[s] significant limitations associated with [gene therapy] . . . when used alone*" (specification at [025]) and, in fact, "tak[es] advantage of the strengths and address[es] the weaknesses associated with [gene] therapy employed alone." Specification at [033] (emphasis added).

Applicants submit that the Examiner fails to acknowledge the significant body of literature and US patent disclosures that *do* present evidence of therapeutic successes

[3] A lack of animal models was cited in Wraith 2006 as a problem in the 1970's, not at applicants' filing date in 2004.

in animals. In addition to the many references and patents provided by Applicants' response to the June 1, 2007 Office Action, numerous additional patents were granted by the USPTO before the priority date of the present application providing methods for performing gene therapy. *See, e.g.*, U.S. patents listed in the table below.

Patent No. Issue Date	Title/Abstract/Claim
4,396,601 Aug. 2, 1983	**Gene Transfer in Intact Mammals** Methods and compositions are provided for gene transfer to intact mammals with expression of the exogenous genetic material in the host. Mammalian host cells which are regenerative, normally highly proliferative or subject to induced proliferation, are transformed or modified *in vitro* with DNA capable of replication and expression in the host cell, wherein the DNA becomes incorporated into the cell. The modified cells are found to regenerate in the host with expression of the introduced DNA. Particularly, mammalian cells were modified with genes providing for overproduction of a particular enzyme. The modified cells were reintroduced in the host under conditions providing for selective advantage of the modified cells. 1. A method for introducing into a mammalian host exogenous genetic capability capable of expression in said host, which comprises: isolating cells from a mammal or a syngeneic equivalent, where cells are from a regenerative body member to provide parent cells; combining said parent cells with DNA, including at least one gene capable of providing a selective advantage over the parent cells, when said parent cells are subjected to mitotic inhibition, under conditions where said DNA is introduced into said parent cells by other than cell-cell fusion to provide modified cells; introducing said modified cells into said host, wherein said modified cells return to said body member of said parent cells; and administering to said host said mitotic inhibitor to provide a selective advantage for said modified cells over said parent cells, whereby said modified cells regenerate in said host.
4,866,042 Sept. 12, 1989	**Method for the Delivery of Genetic Material Across the Blood Brain Barrier** A method for treating genetic and acquired brain disorders is disclosed in which genetic material is introduced into the blood stream for delivery to the brain. Prior to delivery, the interendothelial structure of the BBB is chemically altered to permit passage of the genetic material therethrough. This is accomplished through osmotic disruption of the BBB by administration of suitable chemical agents. Prior to administration, the genetic material can be inserted within the genome of a viral vector preferably incapable of replication *in vivo*. After crossing the blood brain barrier, the vector containing the genetic material enters the brain tissues where it delivers in a site-specific manner the genetic material in order to control adverse effects of the disease caused by defective genes. After delivery of the genetic material, the replication-defective character of the viral vector prevents its reproduction. 1. A method for the delivery and incorporation of corrective genetic material into the cellular tissues of the brain of a human subject or other warm blooded animal subject for the treatment of genetic and acquired metabolic brain disorders, the method

	comprising the steps of: inserting genetic material designed to correct disorders of the brain into a virus; chemically disrupting the blood brain barrier of the subject so as to increase the permeability thereof; administering said virus containing said genetic material into the bloodstream of said subject for incorporation into the cellular tissues of said brain, said virus crossing the blood brain barrier of its increased permeability; and allowing said virus to deliver said genetic material into said cellular tissues of said brain, said genetic material being incorporated into said cellular tissues in order to treat said disorders of said brain.
5,693,536 Dec. 2, 1997	**Gene Therapy with MCC** A new human gene termed MCC is disclosed. Methods and kits are provided for assessing mutations of the MCC gene in human tissues and body samples. Gross rearrangement and point mutations in MCC are observed in human tumor cells. MCC is expressed in most normal tissues. These results suggest that MCC is a tumor suppressor. 1. A method of supplying wild-type MCC gene function to a cell which has lost said gene function by virtue of a mutation in an MCC gene, comprising: introducing a wild-type MCC gene into a cell which has lost said gene function such that said wild-type MCC gene is expressed in the cell.
6,001,816 Dec. 14, 1999	**Gene Therapy for Leptin Deficiency** Gene therapy can treat obesity in mammals. An adenoviral vector encoding a leptin gene is delivered intravenously to a mammal with a deficiency in functional leptin to decrease weight, decrease serum insulin levels or decrease serum glucose levels. 1. A method of treating obesity in a mammal having a deficiency in functional leptin comprising administering intravenously to the mammal an adenoviral vector comprising a DNA sequence encoding a leptin operably linked to a promoter and expressing the DNA sequence, wherein the mammal exhibits a decrease in body weight, a decrease in serum glucose levels and/or a decrease in serum insulin levels.
6,054,288 Apr. 25, 2000	***In vivo* Protein Production and Delivery System for Gene Therapy** The present invention relates to transfected primary and secondary somatic cells of vertebrate origin, particularly mammalian origin, transfected with exogenous genetic material (DNA) which encodes a desired (e.g., a therapeutic) product or is itself a desired (e.g., therapeutic) product, methods by which primary and secondary cells are transfected to include exogenous genetic material, methods of producing clonal cell strains or heterogenous cell strains, methods of gene therapy in which the transfected primary or secondary cells are used, and methods of producing antibodies using the transfected primary or secondary cells. The present invention includes primary and secondary somatic cells, such as fibroblasts, keratinocytes, epithelial cells, endothelial cells, glial cells, neural cells, formed elements of the blood, muscle cells, other somatic cells which can be cultured and somatic cell precursors, which have been transfected with exogenous DNA which is stably integrated into their genomes or is expressed in the cells episomally. The exogenous DNA either encodes a product, such as a translational product (e.g., a protein) or a transcriptional product (e.g., a ribozyme or an anti-sense nucleic acid sequence) which is a therapeutic product or is itself a therapeutic product (e.g., DNA which binds to a cellular regulatory protein or alters gene expression). 1. A method of providing a therapeutic product in an effective amount to a mammal, comprising the steps of:

	a) obtaining a source of primary cells from a mammal; b) transfecting primary cells obtained in (a) with a DNA construct comprising exogenous DNA encoding the therapeutic product and additional DNA sequences sufficient for expression of the exogenous DNA in the primary cells, thereby producing transfected primary cells which express the exogenous DNA encoding the therapeutic product; c) culturing a transfected primary cell produced in (b), which expresses the exogenous DNA encoding the therapeutic product, under conditions appropriate for propagating the transfected primary cell which expresses the exogenous DNA encoding the therapeutic product, thereby producing a clonal cell strain of transfected secondary cells from the transfected primary cell; d) culturing the clonal cell strain of transfected secondary cells produced in (c) under conditions appropriate for and sufficient time for the clonal cell strain of transfected secondary cells to undergo a sufficient number of doublings to provide a sufficient number of transfected secondary cells to produce an effective amount of the therapeutic product; and e) introducing transfected secondary cells produced in (d) into a mammal in sufficient number to provide an effective amount of the therapeutic product to the mammal.

Issued patents carry a presumption of validity. 35 U.S.C. § 282. Consequently, the issued patents are also presumed to provide enabling disclosures for their claims. Clearly, in spite of some degree of unpredictability in the art of gene therapy, non-enablement of claims involving gene therapy cannot be merely presumed, particularly where, as here, the Examiner is in possession of direct evidence of efficacy of the claimed treatment.

The Examiner relies on statements in *Wraith 2001* and *Eto* as alleged evidence for lack of enablement of gene therapy for lysosomal storage disorders and argues that *Salvetti* only speculates that lysosomal storage disorders may be a good model for gene therapy but does not provide evidence to enable the claims. Office Action at 9-10. Applicants' working examples and submission of four references providing direct evidence that gene therapy can be used to treat lysosomal storage disorders as claimed, renders the Examiner's contentions regarding *Salvetti* irrelevant. Nothing in *Wraith* 2001 or *Eto* negates the enablement of Applicants' claims.

1) Enzyme Sequences

The Examiner contends that use of different lysosomal enzyme sequences in ERT or gene therapy is not enabled. Office Action at 9. Specifically, the Examiner argues that biological functions of proteins are not predictable from mere amino acid sequence and that persons skilled in the art would require undue experimentation to identify the biological function of various lysosomal hydrolases, their variants, and their therapeutic effect in treating various lysosomal storage disorders *in vivo*. To support this argument, the Examiner relies on *Rudinger*, *Kaye*, and *Skolnick*, articles that have nothing to do with lysosomal hydrolases or how they function in lysosomal storage disorders, and ignores the vastly more relevant references previously cited by Applicants. Applicants submit that the Examiner's position is supported by neither the evidence of record, nor the law.

A skilled artisan would have no difficulty selecting an appropriate sequence, which would typically be the wild-type sequence or a close variant, for use in ERT or gene therapy. Indeed, the sequences of lysosomal hydrolases were well known as of the priority date. *See, e.g.*, *Salvetti* at page 106 ("The gene corresponding to the affected enzyme has been identified for most LSD[s] and cDNAs are available . . . ."); *Neufeld* (previously submitted) ("The cloning and characterization of nearly 20 complementary DNAs (cDNAs) and a half dozen genes encoding lysosomal enzymes have been reported to date."); *Pastores* at page 897 ("Most of the genes encoding lysosomal enzymes have been cloned, and the size of the corresponding cDNAs is generally compatible with their transfer by recombinant vectors.").

The Examiner's arguments are all the more off target because the claims are not directed to any gene or amino acid sequences *per se*. Instead, the claims require only the use of these sequences in the methods of treating lysosomal storage disorders. Applicants' claims are analogous to those at issue in *Monsanto v. Scruggs,* 459 F.3d 1328 (Fed. Cir. 2006). There, the defendant argued that the patent-in-suit was invalid for lack of enablement because no particular gene sequence was recited in the claims. The Federal Circuit disagreed, however, and found that the specification adequately enabled the claims.

> [B]ecause of the level of skill in the art and the publicly available information about CaMV, no specific gene sequence needed to be claimed for someone of ordinary skill in the art to understand how to make and use the invention. . . It is true that in some cases specific DNA sequences may be required to satisfy the enablement requirement, namely where the level of skill in the art is low and there is little publicly available information about that DNA. Here, however, specific sequences are not required because CaMV is well-known and well-documented.

Id. at 1338.

Applicants submit that lysosomal storage disorders have been studied for more than 100 years (specification at [004]), that persons skilled in the art have a high level of skill and knowledge about the lysosomal hydrolases involved in these disorders, and that lysosomal hydrolase sequence information was widely available as demonstrated above. Therefore, like the situation in *Monsanto v. Scruggs*, *supra,* where the level of skill in the art is high and publicly available information is abundant, persons skilled in the art would not require undue experimentation to practice the claimed invention merely because specific sequences are not recited in the claims.

2) Vector Constructs

The Examiner discusses *Ziegler*'s use of Ad2/CEHalpha-Gal and Ad2/CMVH1alpha-gal vectors for gene therapy in Fabry mice, *Barbon*'s use of AAV8 vectors for gene therapy in Niemann-Pick mice, and *McEachern*'s use of AAV8 vectors for gene therapy of Gaucher mice, previously cited by Applicants, and contends that they do not provide evidence that the claimed invention is enabled. Specifically, the Examiner argues that the vectors used in these references are "different from those in the instant invention" and that different promoters, enhancers, and vectors could result in different levels of expression of the gene product with a different effect *in vivo*. Office Action at 6 and 7. Applicants submit that the Examiner's arguments again miss the point.

First, Applicants note that the Examiner's comments are directed to *Ziegler 1999*, not *Ziegler 2004,* which was relied upon by Applicants.[4] *Ziegler 1999* describes the use of an Ad2 adenoviral vector and thus, is not covered by Applicants' claims, which recite the use of an AAV gene therapy vector.

Ziegler 2004 describes the use of use of an AAV2 vector harboring a liver-restricted promoter (AAV2/DC190-αgal) to express α-galactosidase in a mouse model of Fabry disease. *Barbon* teaches the use of AAV1 and AAV8 vectors (AAV1/DC190-hASM and AAV8/DC190-hASM) to express human acid sphingomyelinase in a mouse model of Niemann-Pick disease. And *McEachern* discloses the use of AAV8/DC172-hGC to express glucocerebrosidase in a mouse model of Gaucher disease. The

[4] Applicants note that on page 11 of the response filed on Dec. 3, 2007, Applicants referred the Examiner to Ziegler et al., *Mol. Ther.* 9:231-240 (2004) ("*Ziegler 2004*"). *Ziegler 1999* is not relied upon to support enablement.

specification exemplifies the use of AAV2/DC190-αgal to express in a mouse model of Fabry disease. Each of these disclosures demonstrates that an adeno-associated viral (AAV) vector under the control of one or more liver-specific regulatory elements is capable of expressing a lysosomal hydrolase in an animal model of a lysosomal storage disease and inducing an immune tolerance to the expressed enzyme. Consequently, each of these references describes an embodiment covered by the claims and establishes efficacy of the claimed methods. Contrary to the Examiner's suggestion that the use of different promoter/regulatory combinations than those specifically exemplified in the specification cannot provide evidence that the claimed invention is enabled, *Barbon* and *McEachern* provide significant evidence that different AAV vectors and even different liver-restricted enhancer/promoters can be used to treat various lysosomal storage disorders via gene therapy in combination with enzyme replacement therapy. In addition, these references also demonstrate that it is well within the skill of a person in the art to select an appropriate vector and promoter for use in the claimed invention without undue experimentation. Consequently, rather than failing to evidence enablement, these references clearly establish that the full scope of the claims is enabled.

With respect to the potential for different levels of gene product expression, the Examiner has not provided any credible argument as to how this negates enablement.[5] There is no evidence of record that different levels of lysosomal hydrolase expression

[5] One of skill in the art would not expect all vector/promoter combinations falling within the scope of the claim to produce exactly the same level of lysosomal hydrolase expression any more than one would expect all members of a chemical genus to have exactly the same level activity.

would disrupt the immuno-tolerizing effect of the gene therapy component of the claimed methods. In fact, the specification and references establish just the opposite, by competently inducing an immune tolerance to the replacement enzyme in the respective animal model in spite of different levels of expression. To further support enablement of the claimed invention, Applicants submit *Ziegler 2008*, published in June 2008. This reference provides evidence that the claimed invention can be used equally well to treat Pompe disease. This reference could not have been provided to the Examiner earlier because it was not published until after the final rejection was issued. *Ziegler 2008* reports the administration of AAV8/DC190-GAA encoding human acid α-glucosidase to Pompe mice and the animals' subsequent immune tolerization to the expressed lysosomal hydrolase.

3) Administration Routes

The Examiner contends that the administration route of an expression construct plays an important role in gene transfer *in vivo*. Specifically, the Examiner alleges that "[t]he fate of [the] DNA construct, the amount of DNA [that] reaches its targeted site, the stability of the mRNA and protein expressed, and the biological function of the protein all depend on the administration route in gene transfer *in vivo*. Office Action at 4. It appears that the Examiner believes that *Ziegler*, *Barbon*, and *McEachern* reference only provide evidence of enablement for gene therapy administered by tail vein injection, and that other administration routes, "such as oral and topical administration" routes to treat visceral organs, are not adequately taught by the specification. Office Action at 7.

Applicants note that oral gene therapy generally does not involve viral vectors and thus, would not fall within the scope of the claims. Topical administration of gene

therapy may involve a viral vector, but is most often considered for localized treatments. It can, however be used for systemic therapy. See, e.g., U.S. Patent Application No. 11/713,291, entitled COMPOSITIONS AND METHODS FOR TREATING CYSTIC FIBROSIS, and first filed in 2004. Claim 14 of this patent application specifically recites topical administration of an AAV vector to treat cystic fibrosis. Thus, with the knowledge that AAV vectors can be used for topical gene therapy, and the evidence previously provided regarding effective gene therapy using AAV vectors encoding a lysosomal hydrolase under the control of at least one liver-specific regulatory element, Applicants submit that topical gene therapy using the methods of the invention is within the skill of the art.

The Examiner acknowledges that methods of administration were known in the art but contends that Applicants have not enabled their use. Office Action at 11-12. This contention is inconsistent with M.P.E.P. 2164.01(c), which states that if "the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." If the methods of administration are known, then it follows that persons skilled in the art would be able to use them in practice of the invention without undue experimentation. Thus, Applicants' methods are necessarily enabled with respect to the routes of administration.

4) Specific Tissue Targeting

The Examiner contends that the claimed treatments are unable to target specific sites of pathology, especially the CNS. Office Action at 5. The Examiner acknowledges that claim 1 recites a liver-specific regulatory element but questions how the liver-

specific regulatory sequence would be able to provide sufficient expression of desired lysosomal hydrolase in cells and organs other than liver. Office Action at 10.

Applicants again note that the Examiner has ignored the evidence of record. Each of the references discussed above (in the section on vector constructs) specifically discloses correction of metabolic defects in the *visceral organs* of mouse models of LSD. Thus, the evidence of record demonstrates that, despite limiting expression of lysosomal hydrolase mRNA to the liver (*see* specification at [0203]), the expressed lysosomal hydrolases are still circulated within the body and are found at sites other than the liver.

For example, in Example 5, at paragraph [0199] of the specification as well as at page 233, Col. 1 of *Ziegler 2004*, the use of the liver-restricted enhancer/promoter DC190 was shown to provide 15-fold greater expression of α-galactosidase in the liver of BALB/C mice than with the use of a non-liver restricted enhancer/promoter. Correspondingly higher levels of the hydrolase were also detected *in the serum, hearts and kidneys* of these mice. Accordingly, both the specification and *Ziegler 2004* illustrate expression of lysosomal hydrolase in various organs and in serum.

Ziegler 2008 at page 612, Figure 1, demonstrates increased levels of α-glucosidase in the serum, diaphram, heart, quadriceps, and triceps of Pompe mice after systemic administration of AAV8/DC190-GAA.

McEachern reports at page 723 that "hepatic secretion of the enzyme into circulation resulted in lung and spleen enzyme levels that approached that of approximately 50% of normal levels and Figure 2A demonstrates elevated expression of

glucocerebrosidase in serum, liver, spleen, and lung of a Gaucher mouse model after administration of gene therapy vector AAV8/DC172-hGC.

Barbon at page 433, Figures 1 and 2, provides evidence that gene therapy using AAV and a liver specific promoter to express human acid sphingomyelinase, results in increased levels of the lysosomal hydrolase in the liver, spleen, lung, kidney, and serum of a mouse model of Niemann-Pick disease and at page 434, *Barbon* reports that "[t]hese data indicated that AAV8-mediated expression of acid sphingomyelinase was efficacious at reversing the pathology in the most severely affected *visceral organs* in the [acid sphingomyelinase knockout] mice" (emphasis added).

Moreover as emphasized above, the claimed methods are *combination* treatments comprising administering a gene therapy vector encoding a lysosomal hydrolase and then administering an exogenously produced lysosomal hydrolase. Combination therapy takes advantage of the strengths and addresses the weaknesses associated with each individual therapy alone. Specification at [033]. In addition, if one therapy does not provide adequate levels of a lysosomal hydrolase, again, the other therapy will compensate for the shortfall. In addition, initial gene therapy can reduce any immune response induced by ERT. Specification at [0208] - [0209].

And as also emphasized above, even if a method of treatment does not reach all areas of a patient's body, the claimed methods of treatment can still ameliorate some symptoms, stabilize a patient's condition, prevent deterioration, increase life expectancy, or otherwise improve a patient's quality of life. Thus, Applicants submit that the Examiner's concerns regarding targeting specific sites of pathology are unfounded.

In light of the foregoing, Applicants submit that the field of gene therapy, particularly as applied to lysosomal storage disorders, was adequately developed as of the priority date of the present application to enable the invention as claimed.

Guidance and Working Examples

Applicants submit that the specification provides adequate guidance to persons skilled in the art to practice the claimed invention. The specification provides information about lysosomal storage disorders, the enzyme deficiency involved and the resulting accumulated metabolite. Paragraphs [004] - [012], [086], [099] - [0101], and [0103] - [0104]. The specification provides detailed information about gene therapy for lysosomal storage diseases (paragraphs [014] - [017], and [0120] - [0124]), enzyme replacement therapy (paragraphs [018] - [020] and [0155] - [0157]) adeno-associated viral vectors (paragraphs [0130] - [139], tissue specific promoters and enhancers (paragraphs [0179] - [0183]), including liver specific promoters (paragraphs [0181] - [0183]), dosing regimens (paragraphs [099] - [0101], [0106], [0108], [0110], [0112], [0114], [0169] - [0178]), and methods for monitoring disease progression (paragraphs [0104], [0115], [0117] - [0119]). Working Examples 2-9 demonstrate successful treatment of Fabry disease in accordance with the claimed invention. Examples 10-12 disclose methods of treating Pompe disease with combination gene and enzyme therapy. Applicants additionally submit that the work reported by *McEachern, Barbon, Ziegler 2004, and Ziegler 2008* following the teachings of the specification, demonstrates both the efficacy of the claimed invention for the treatment of four distinct lysosomal storage disorders and the adequacy of the guidance provided by the specification.

Applicants submit that the specification provides adequate guidance to persons skilled in the art to practice the claimed invention without undue experimentation.

Predictability

The Examiner contends that the state of the art of treating lysosomal storage disorders was unpredictable at the time of the invention. Office Action at 4. In particular, the Examiner contends that due to the diversity of lysosomal storage disorders, the broad heterogeneity in clinical expression of lysosomal storage disorders, the prospect of partial treatment, the inability to target specific sites of pathology, especially the CNS, and the lack of suitable animal models of the human disease to evaluate new therapy, the claims are not enabled. Applicants traverse.

The Examiner cites to *Pastores*, *Wraith 2001*, and *Eto* to support his contention that "the state of the art of treating lysosomal storage diseases" was "unpredictable" in 2004. Applicants submit that the Examiner may have misread these articles. The first sentence of *Pastores* states that [t]argeted treatments for the lysosomal storage disorders (LSDs), in the form of enzyme replacement and/or substrate depletion have been shown to be relatively safe and effective in reversing core disease features in selected clinical subtypes (including Gaucher disease types I and III, Fabry disease and the Jurler-Scheie syndrome)." *Pastores* also states (at page 895, Col. 2) that "[t]he favorable therapeutic profile of ERT for GD, FD, MPS I (Hurler-Scheie syndrome) and MPS IV has made the corresponding recombinant enzyme treatments either the current standard of care or the preferred first-line option in the management of these disorders." In addition, far from suggesting that gene therapy for LSDs is unpredictable, *Pastores* provides a very positive review of the work being done at that time -- suggesting that

"animal studies raise hopes for gene therapy clinical applications in the foreseeable future." See, page 897, Cols. 1 and 2.

Similarly, *Eto* states in the Summary at page 411 that "[f]or gene therapy to the CNS, a recombinant adenovirus encoding β-galactocerebrosidase gene was injected into the cerebral ventricle of neonatal twitcher mice, a murine model of Krabbe disease. Improvements in neurological symptoms and a prolonged lifespan were observed." There is no statement or even suggestion in *Eto* that treatment of lysosomal storage disorders is unpredictable. Likewise, *Wraith 2001* indicates that even years before Applicants' filing date, "significant progress" had been made in the treatment of lysosomal storage disorders. Page 644, Col. 2.

Consequently, Applicants submit that the art of treating lysosomal storage disorders is not nearly as unpredictable as the Examiner contends. Those of skill in the art believe that current and past treatments have been successful . Further, in view of state of the art at Applicants' filing date, those of skill in the art appear to expect that treatment of additional lysosomal storage disorders will be successful.

Conclusion

Applicants submit that the Examiner's enablement rejection is improper in view of the evidence of record and respectfully request withdrawal of the rejection and allowance of the claims. Applicants respectfully request reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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